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(57) Abstract

A gum composition which comprises a gum base which has a water content of less than 2 % by weight of the final composition characterised in that the composition contains an antibacterially effect amount of a bacteriocin antibacterial agent. The compositions are useful in antiplaque and breath freshness therapy.

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A CHEWING GUM COMPOSITION CONTAINING A BACTERIOCIN ANTIBACTERIAL AGENT

This invention relates to oral hygiene compositions and in particular to oral hygiene gums comprising particular antibacterial agents which compositions are useful in antiplaque and breath freshness therapy.

A particular class of antibacterial agents are the bacteriocins. These have been defined as proteinaceous substances produced by bacteria and which have antibacterial activity only against species closely related to the species of origin. More recently it has been found that, at least in certain instances, the spectrum of antibacterial activity may in fact be broader.

An example of a bacteriocin which has already found commercial application is nisin. This is a lanthocin, comprising the atypical amino acid lanthionine. Nisin is a polypeptide with antibacterial properties which is produced naturally by various strains of the bacterium *Streptococcus lactis*. It is also a naturally occurring preservative found in low concentration in milk and cheese. Nisin has recently been recognised by the FDA as a direct food ingredient. A summary of nisin's properties is to be found in Advances in Applied Microbiology 27 (1981), 85-123.

Recently, a purified form of nisin has been made available by Applied Microbiology Inc under the trade name AMBICIN N®. It has been suggested for use in a variety of applications including oral care, as disclosed in PCT Application WO 89/12399 to Blackburn et al., and now in issued US Patent No. 5,135,910 for use in the oral cavity, however the only specific disclosure of an oral hygiene product is as an oral rinse, for use as a broad spectrum disinfectant. UK Application 9510719.9 discloses a nisin oral care compositions for controlling *Candida* as well as previously indicated antibacterial activity against plaque and gingivitis. There is no reference in any of the abovementioned patents or applications to gum formulations containing nisin or AMBICIN N®.

The formulation of compositions comprising highly purified proteins, such as the compound nisin, are particularly challenging as a protein in this state is rendered sensitive to many of the processes that are commonly required in the preparation of successful formulations.

These problems are highlighted in 'Stability of Protein pharmaceuticals' part B, *In vivo* Pathways of Degradation and Strategies for Protein Stabilization, Edited by Tim J. Ahern and Mark C. Manning.

Chewing gum compositions are, in general, composed of a water-insoluble or base component and a water-soluble chewing gum component, and as a result it is known that moisture loss and gain can effect the life of gum products.

Chewing gum compositions which have low moisture content and/or low moisture pickup during storage are known. EP-A-0472 428 (WM Wrigley JR.Company) describes a low moisture gum which includes about 30 to 90% of a gum base with a softening point from about 70°C to about 100°C; from about 0.1 to about 20% of a water-insoluble plasticizer; from about 0 to 65% solid bulk sweetener; less than about 0.5% water; and is substantially free of humectant. EP-A-0328 849 (Warner-Lambert Company) claims a sugarless, anhydrous chewing gum composition having a low-moisture pick-up which includes from about 10 to 75% of a gum base, a low-moisture pick-up bulking agent which both inhibits moisture pick-up and provides enhanced firmness, and a high intensity sweetener. Preferably the low-moisture pick-up bulking agent is an isomalt.

It has thus been found that when a gum, in particular an oral healthcare gum which contains bacteriocin derivatives, particularly nisin, is prepared by applying usual, conventional formulations and known processes, an unacceptable, unstable product results. In such cases the antibacterial agent will break down during processing and further on storage.

It has also been found that use of a water soluble purified protein, such as nisin, in a gum composition can be released in a controlled and sustained manner to provide extended antibacterial activity. Nisin also benefits as a protein moiety, from being a safe and ingestible active material.

It has therefore become desirable to prepare a gum composition which does not possess the instability problems associated with the use of nisin and that is stable and acceptable to the consumer, thus increasing its shelf life. By careful selection, control and order of addition of the ingredients that make up the composition it has been possible to prepare a gum containing the active bacteriocin derivatives.

Accordingly, the present invention provides a gum composition which comprises a gum base and has a water content of less than 2% by weight of the final composition characterised in that the composition contains an antibacterially effect amount of a bacteriocin antibacterial agent.

In a further aspect of the invention there is provided a gum composition which comprises a gum base and an antibacterially effect amount of a bacteriocin antibacterial agent and which has a water content of from 1.0 to 1.5% by weight of the final composition.

The gum compositions of the present invention are considered anhydrous or substantially anhydrous compositions as they have moisture contents of below 2%, preferably 1.5%, and most preferred 1.0% by weight of the final gum composition. It is only by use of this very low moisture content in the composition that it possible to achieve a gum containing AMBICIN N® that is acceptably stable. Therefore in accordance with the present invention, moisture (in the form of water) is all but entirely removed from the compositions, and in as many cases as possible, materials in their powder or anhydrous form are incorporated in the compositions.

Suitable bacteriocin antibacterial agents include nisin, gramicidin and tyrothricin and purified forms of bacteriocins such as AMBICIN N®. Nisin and in particular the purified nisin preparation, in the form of AMBICIN N®are especially preferred. AMBICIN N® may be used in the encapsulated form to protect against degradation, for example by embedding in a carbohydrate glass such as the sugar trehalose.

In compositions of the present invention, the gum comprises from 0.001 to 5.0%, preferably from 0.005 to 2.0%, advantageously from 0.02 to 1.0 % of bacteriocin antibacterial agent by weight of the final composition. In an alternative manner the level of bacteriocin agent needed is one which reaches a sufficient level in the oral cavity to inhibit the desired microrganisms. An effective level of a bacteriocin agent in the oral cavity, and more specifically nisin, to inhibit the desired organisms is a level of about 0.99 ppm.

With regard to the gum composition the amount of gum base employed will vary depending on various factors such as the type of base used, consistency required in the final product

and the other components used in the composition. A typical gum base composition comprises elastomers, resins, fillers and softeners. The gum base will be selected from those commercially available. The elastomer component of the gum base can be selected from, but not limited to, synthetic elastomers for example styrene-butadiene copolymer, isobutylene-isoprene copolymer, polyisobutylene, and natural elastomers like chicle, natural rubber and jelutong and mixtures thereof.

The gum base usually includes a resin which acts as an elastomer solvent and can be selected from terpene resins, glycerol esters of hydrogenated, partially hydrogenated, polymerised and partially dimerised rosin and mixtures thereof. The resins may be used in an amount of from 10 to 50% by weight of the gum base. Fillers such as talc, calcium carbonate and magnesium silicate in quantities of from 20 to 50% by weight of the gum base may also be present in the gum base. In this particular invention, talc is the preferred filler. The gum base may also include if desired, softeners, texture modifiers such as waxes, partially hydrogenated vegetable oils and emulsifiers, particularly useful being lecithin, fatty acid mono, di and triglygerides, glycerol monostearate and triacetin in amounts of about 5% by weight of the gum base. Other optional ingredients include antioxidants, preservatives and colorants.

The gum base may be either a soft or a hard gum base with no subsequent restriction on the softening point temperature. Typically a soft gum base would be for example a bubble gum and a hard gum would be a medicated gum. Suitably a hard gum base is used in the present invention. Suitably the gum base will be present in the amount of from 10 to 70%, preferably from 15 to 45% and most preferably from 30 to 40% by weight of the final composition.

Compositions of the present invention will include at least one sugar alcohol (polyols) ingredient, used as non-sugar bulk sweetener, as particularly in the instance of sugar-free gum compositions. The sugar alcohols include sorbitol, xylitol, mannitol, lactitol and maltitol. Hydrogenated glucose syrup, which is known by the Trade name Lycasin or polyhydric alcohols such as glycerine or mixtures thereof may also be used as bulk sweeteners. The exact selection of the bulk sweetener will be determined by the required texture of the final gum to meet processing requirements, product stability and consumer

acceptance criteria. Particle size is important in controlling elasticity and firmness, especially in low moisture compositions.

Suitably the sugar alcohol will be present in the range of from 15 to 70%. preferably from 25 to 65% and more preferably from 55 to 65% by weight of the final composition.

When sorbitol is used as the sugar alcohol either alone or in combination thereof, it may be incorporated in either the liquid or the anhydrous powder form. Liquid sorbitol is sold as a 70% aqueous solution, therefore if the liquid form is to be used in the composition, it will be necessary to keep the level as low as possible, thus excluding as much water as possible from the final composition, but in anycase keeping the moisture content below the critical value of 2.0% by weight of the final composition.

When hydrogenated glucose syrup is used as the bulk sweetener either alone or in combination thereof, suitably it will be present in the range of from 0.1 to 5.0%, preferably from 2.0 to 3.5%, most preferably 3.0% by weight of the final composition.

The gum composition according to the present invention may contain a variety of flavours alone or in admixture. Particularly suitable flavours include essential oils, such as cinnamon, spearmint, peppermint and the like and synthetic flavours. Natural flavours, for example those derived from the essence of fruits may also be used. The flavour can be a liquid and/or powder form to give a long lasting effect. Sweetening agents, for example sodium saccharin, Aspartame, Acesulpham K, Neohesperidine Dichalconate and Talin and solubilisers such as lecithin and Cremophor (polyethoxyhydrogenated castor oil) which is a Tradename of BASF, may be added to the composition to help release and modify flavour. Suitably any flavour that is used in the present invention will be added in the range of from 0.1% to 3.0% by weight of the final composition.

Selection of flavour and solubiliser may also modify the texture of the gum composition. Additions of vegetable oils may also be used to keep the gum soft. These oils may be incorporated at levels of 0.5 to 3% by weight of the final composition.

In a preferred aspect, compositions according to the present invention comprise a gum base; one or more sugar alcohols such as, for instance, sorbitol and xylitol; flavour and AMBICIN N®. Glycerine is to be avoided or minimised in such compositions.

Compositions according to the present invention may usefully comprise a fluoride ion source, to provide an anti-caries activity. A fluoride ion source is found to be compatible with the bacteriocin peptide antibacterial agent. Suitable fluoride ion sources include metal fluoride salts, for instance alkali metal fluoride salts such as sodium fluoride, amine fluoride salts, alkali metal monofluorophosphate salts such as sodium monofluorophosphate and amine monofluorophosphate salts. Suitably the fluoride ion source would, if present, be included to provide from 50 to 3500 ppm, preferably 100 to 2500 ppm of fluoride ions.

The gum composition may also comprise further optional ingredients may be added to the composition such as buffering agents, for example urea and bicarbonate, dyes, pyrophosphates, whitening agents, for example titanium dioxide and sodium tripolyphosphate (STP), preservatives, chelators to broaden the spectrum of activity, for example ethylenediaminetetraacetic acid (EDTA) and citrate, antisensitivity agents such as strontium and potassium salts, polishing agents and anticalculus agents such as tetraalkali and dialkaliimetal pyrophosphate salts. It will be appreciated that in each instance, an optional ingredient, if included, will be compatible with the bacteriocin.

The gums according to the present invention may be either sugar-free or sugar containing. Sweeteners are well known in the art and include sugars such as sucrose, glucose, dextrose and mixtures thereof. In instances where a sugar-free containing gum is required, auxiliary sweeteners are incorporated into the compositions. The gums may be presented in any of the presentations as conventionally used in the art, for instance as sticks, strips and dragees.

Compositions according to the invention will have a pH which is orally acceptable and within which the antibacterial activity of the bacteriocin is not substantially compromised. Also citrates, maleates or oxalates may be added as enzyme inhibitors to reduce the fall in plaque pH. Gum compositions according to the invention may be prepared by conventional mixing/kneading procedures, comprising admixing the ingredients together in the appropriate relative amounts in any order that is convenient with the proviso that the nisin must be added during the final step of the procedure and preferably not in aqueous solution.

Suitably, all excipients are dried, such that, for example the gum base, sugar alcohol, flavour and nisin are in the anhydrous form and not in aqueous solution. An example of this process would involve firstly melting the gum base at room temperature, thereafter increasing the temperature to approximately 50 to 60°C. The sugar alcohol, flavour and additives are added thereafter with continuous mixing. Nisin is then added at this final stage of the process, preferably in a premix with any sugar alcohol and at this point the temperature should preferably be between 50 and 70°C. The mixing time after adding nisin should be minimised but sufficient to ensure adequate dispersion. Control of temperature, mixing, sheer and time is important. The gum may then be formed into its desired shape, such as sticks, strips or dragees.

To optimise the shelf life of the gum composition moisture pick up should be avoided or controlled. Hygroscopic humectants may usefully be used in this respect.
The gum composition can be coated inside a candy coating of sucrose or preferably sugar alcohol such as sorbitol, mannitol or xylitol. An intermediate coating can also be used to minimise moisture migration between for example dragee centre and coating. These intermediate coatings include gum arabic, gelatin, and other film forming ingredients like ethyl cellulose and copolymers of methacrylic acid and ethyl acrylate which is sold under the Tradename of Eudragit from Rohn Pharma.

Coatings for gums are well known in the art, but typically when a gum coating is required for a dragee of the present invention this will comprise of approximately 99.63% of sorbitol solution, 0.3% liquid flavour and 0.07% carnuba wax. The weight ratio of gum centre to coating in this instance will be 0.9-1.0g: 0.25-0.35g.

Gum compositions of the present invention are effective against oral bacteria and as such will be of use in antiplaque and breath freshness therapy.

Accordingly, the present invention provides a method of reducing or preventing the formation of dental plaque, which method comprises applying an antiplaque effective amount of a composition according to the present invention to a patient in need thereof.

Accordingly, in a further aspect, the present invention also provides a method of freshening the breath, which method comprises applying a breath freshness effective amount of a composition according to the present invention to a patient in need thereof.
® indicates a registered trademark.

The selection of a composition comprising the water insoluble gum base. the water soluble bulk sweetener and other excipients is made to optimise the release of the antibacterial agent, nisin, over an extended time to provide an exposure time for the active ingredient. See Figs 1 and 2 for this release data.

The invention will also be illustrated by reference to the following examples:

EXAMPLE	1	2	3	4	5	6	7	8
Ingredient	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
Gum Base	35.00	35.00	35.00	35.00	35.00	35.00	36.00	36.00
Xylitol	20.00	20.00	20.00	-	57.00	20.00	20.00	20.00
Sorbitol powder	37.05	36.85	38.30	57.05	-	29.85	37.25	34.85
Sorbitol liquid, 70%	3.00	-	-	3.00	3.00	-	-	-
Liquid flavour	1.75	1.75	2.50	1.75	1.75	1.75	2.50	1.75
Menthol	1.50	1.50	1.00	1.50	1.50	1.50	0.75	1.50
Powder flavour	1.50	1.50	-	1.50	1.50	1.50	-	1.50
Ambicin N	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Lycasin	-	3.00	3.00	-	-	-	3.00	3.00
Mannitol	-	-	-	-	-	10.00	-	-
EDTA	-	0.20	-	-	-	0.20	0.20	0.20
Lecithin	-	-	-	-	-	-	0.10	-
Vegetable fat	-	-	-	-	-	-	-	1.00

1. A gum composition which comprises a gum base and has a water content of less than 2% by weight of the final composition characterised in that the composition contains an antibacterially effect amount of a bacteriocin antibacterial agent.

2. A gum composition which comprises a gum base and an antibacterially effect amount of a bacteriocin antibacterial agent and which has a water content of from 1.0 to 1.5% by weight of the final composition.

3. A composition according to claim 1 or 2, wherein the bacteriocin antibacterial agent include nisin, gramicidin and tyrothricin and purified forms of bacteriocins such as AMBICIN N®.

4. A composition according to claim 3, wherein the bacteriocin antibacterial agents are present in an amount of from 0.001 to 5.0% by weight of the final composition.

5. A composition according to claim 4 wherein the bacteriocin antibacterial agent is AMBICIN N®.

6. A composition according to any one of the preceding claims wherein the gum base is present in an amount of from 10 to 70% by weight of the final composition.

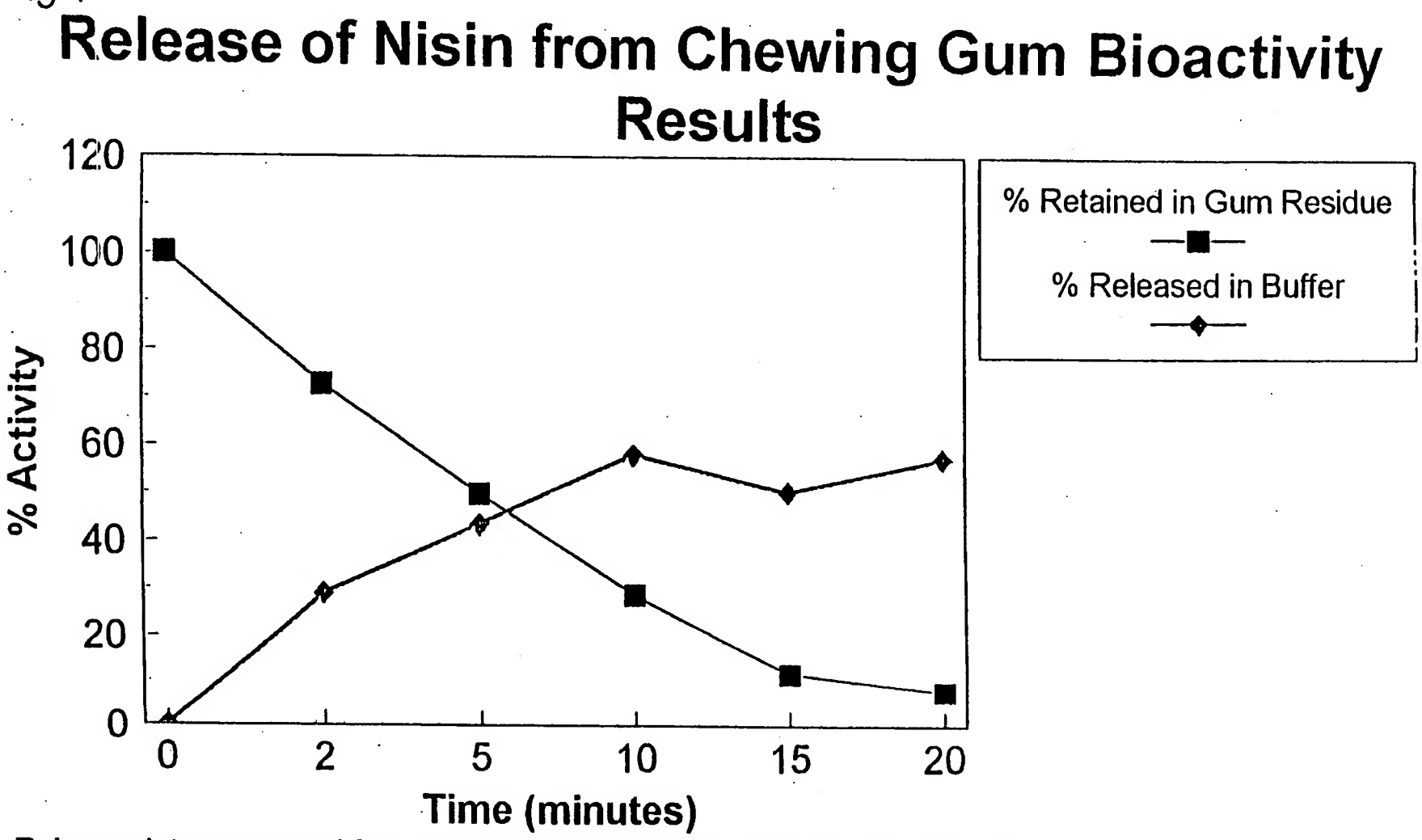
7. A composition according to any one of the preceding claims which additionally comprises a non-sugar bulk sweetener.

8. A composition according to claim 7 wherein the non-sugar bulk sweetener is present in the range of from 15 to 70% by weight of the final composition.

9. A process for the preparation of a composition according to any one of the preceding claims which comprises admixing the ingredients together in the appropriate relative amounts in any order that is convenient with the proviso that the nisin must be added during the final step of the procedure and preferably not in aqueous solution.

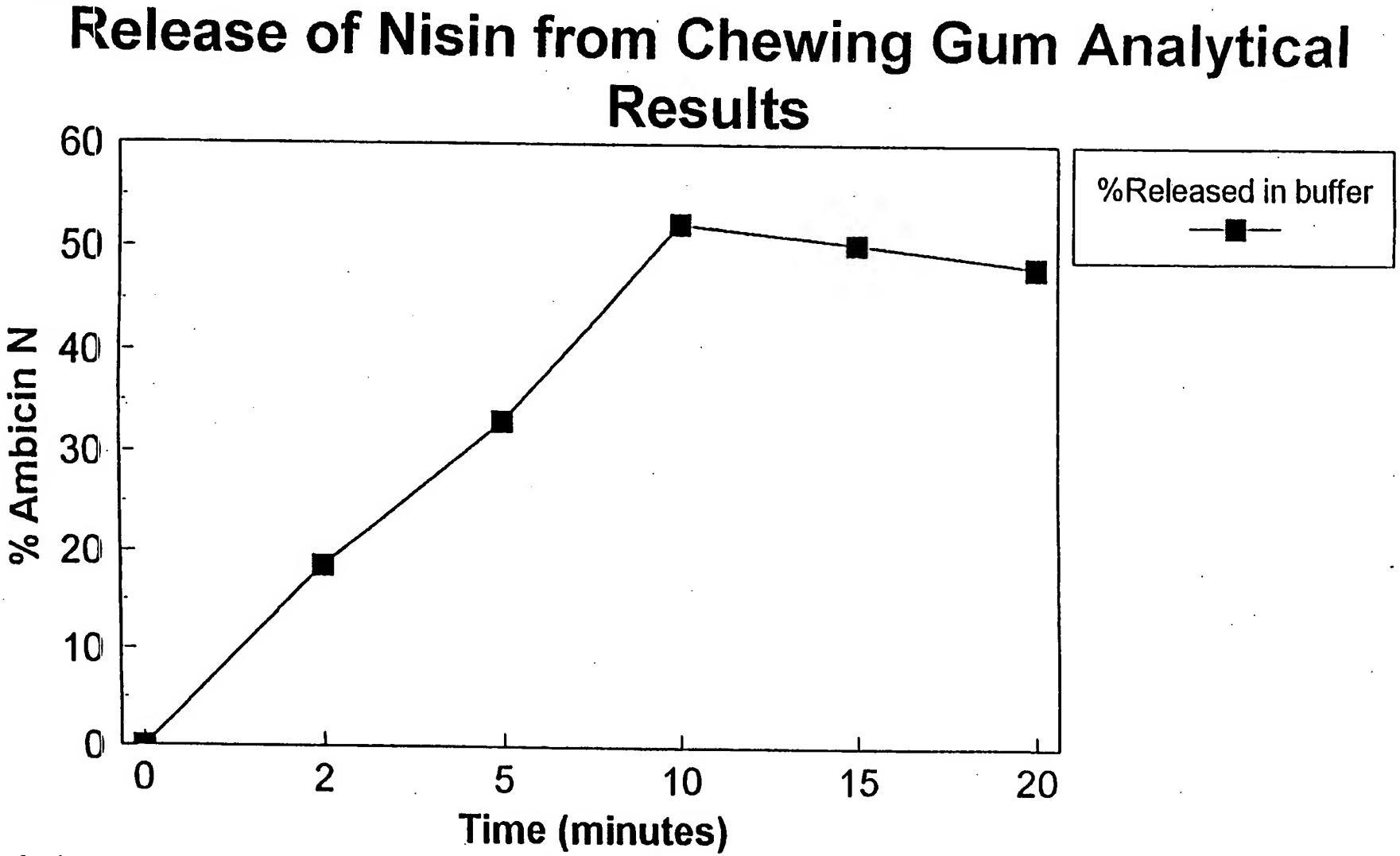
10. A method of reducing or preventing the formation of dental plaque, which method comprises applying an antiplaque effective amount of a composition according to any one of the preceding claims to a patient in need thereof.

Fig 1



Release data generated from chewing simulator and measured by zone of inhibition using M.Luteus

Fig 2



Active measured by reverse phase HPLC

INTERNATIONAL SEARCH REPORT

Inter onal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO,A,94 12150 (SMITHKLINE BEECHAM PLC ;FORWARD GEOFFREY CHARLES (GB); BARTLETT MI) 9 June 1994 see the whole document	1,3-5,9, 10
X	WO,A,94 05251 (LEE DE NV SARA ;TIMMER CHRISTIENA JANNIE (NL)) 17 March 1994 see example 5	1,3,4,10
A	WO,A,93 11738 (SMITHKLINE BEECHAM PLC) 24 June 1993 see the whole document	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
12 December 1996	10. 01. 97

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

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